REMARKS

Claims 1-4, 6, 8-21, 23, 24, 32-39 and 43-48 are pending. By virtue of this response, claims 1, 23, 46, and 47 are amended and no claims are added. Claims 32-39 are withdrawn. Therefore, claims 1-4, 6, 8-21, 23, 24, 32-39 and 43-48 are presently pending.

In order to expedite prosecution, claims 1, 23, 46, and 47 have been amended to provide that the oligonucleotide is at least 6 nucleotides in length and comprises at least one phosphorothioate bond and the CG motif comprises an unmethylated CpG dinucleotide. Support for this amendment may be found throughout the specification including, by way of example, on page 4, lines 9-11, page 5, lines 3-4, and page 8, lines 12-15.

As no new matter has been added with this amendment, entry of this amendment is respectfully requested. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

I. Claim Rejections Under 35 USC §112

Claims 1-4, 6, 8-21, 23, 24 and 43-48 are rejected under 35 U.S.C. 112, first paragraph, as allegedly not being enabling for the claimed scope.

To the extent the rejection is applicable to the amended claims, Applicants respectfully traverse the rejection and its supporting remarks.

i. Features of CG motifs

The Examiner has asserted that the specification is not enabling for "oligonucleotides comprising at least one CG motif" because the recitation is not sufficient to define an oligonucleotide with adjuvant function. The Examiner supports this position by reciting a long list of things that are allegedly not disclosed in the specification. However, MPEP 2163 is clear that enablement does not turn solely upon what is disclosed in the specification:

> See also *United States v. Telectronics, Inc.*,857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent ***coupled with information known in the art*** without undue experimentation."). ***A patent need not teach, and preferably omits, what is well known in the art.*** *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). (emphasis added).

Thus, it is clear that the Applicants do not need to disclose every possible facet of the CG motif.

A. A Great Deal of Information was Known in the Art Regarding CG Motifs

Oligonucleotides comprising at least one CG motif were a known class of adjuvants as of the effective filing date. This class of adjuvants was known to share a common mode of activity as discussed in the review by Krieg (BioDrugs 1998, 5:341-346). Thus, none of the details cited by the Examiner fundamentally change the nature of the immune response. In other words, there is no subclass of CG motif oligonucleotides that stimulates a T_H2 response. Thus, the details really only go to the magnitude of the immune response that will be stimulated by a given amount of the CG motif oligonucleotide. As long as there is some T_H1 response stimulation, the proper amount may be achieved by titration of the CG motif oligonucleotide.

Furthermore, as demonstrated by the articles cited by the Examiner, there were several sources for ***information known in the art*** which support enablement. These sources provide guidelines for experimental design of suitable CG oligonucleotides adjuvants and were available as of the priority date of the present invention. The specification also provides citations to numerous references regarding such oligonucleotides. By way of example, on page 4, the specification discloses:

> Oligonucleotides comprising CpG motifs mixed with antigens have been demonstrated to induce strong Thl immune responses.

Roman *et al, Nat. Med.*, **1997**, *3*, 849-854; Weiner *et al, Proc. Natl Acad. Sci. USA*, **1997**, *94*, 10833-10837; Davis *et al, J. Immunol*, **1998**, *160*, 870- 876; Chu *et al, J. Exp. Med*, **1997**, *186*, 1623-1631; Lipford *et al, Eur. J. Immunol*, **1997**, *27*, 2340-2344; and Moldoveanu *et al, Vaccine*, **1988**, *16*, 1216-1224, the disclosures of which are incorporated herein by reference in their entirety. Unmethylated CpG dinucleotides are relatively common in bacterial DNA, but are underrepresented and methylated in vertebrate DNA. Bird, *Trends Genet.*, **1987**, *3*, 342-347. Bacterial DNA or synthetic oligonucleotides containing unmethylated CpG motifs are also known to induce immune responses including, for example, B cell proliferation, interleukin-6 and immunoglobulin secretion, and apoptosis resistance. Krieg *et al, Nature*, **1995**, *374*, 546-549; Klinman *et al, Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 2879-2883; Ballas *et al, J. Immunol*, **1996**, *157*, 1840-1845; Cowdery *et al, J. Immunol*, **1996**, *156*, 4570-4575; Halpern *et al, Cell. Immunol*, **1996**, *167*, 72-78; Yamamoto *et al, Jpn. J. Cancer Res.*, **1988**, *79*, 866-873; Stacey *et al, J. Immunol*, **1996**, *157*, 2116-2122; Messina *et al, J. Immunol*, **1991**, *147*, 1759-1764; Yi *et al, J. Immunol*, **1996**, *157*, 4918- 4925; Yi *et al, J. Immunol*, **1996**, *157*, 5394-5402; Yi *et al, J. Immunol*, **1998**, *160*, 4755-4761; and Yi *et al, J. Immunol*, **1998**, *160*, 5898-5906; PCT publications WO96/02555, WO98/16247, WO98/18810, WO98/40100, WO98/55495, WO98/37919 and WO98/52581, the disclosures of which are incorporated herein by reference in their entirety. CpG oligonucleotides, however, have not been shown to induce bactericidal antibody responses.

Thus, the Applicants provide an extensive list of 19 references and 7 PCT patent publications, which were available to those of skill in the art. All of the teachings of these 19 references and 7 PCT patent publications are ***information available in the art*** that support enablement of the claims. Therefore, the state of the art provides sufficient details to assist one of skill in the art to design suitable oligonucleotides comprising at least one CG motif.

B. The Specification Provides Solid Disclosure of CG Motifs

In addition to the numerous articles available to those of skill in the art as of the filing date that teach how to make and use the claimed oligonucleotides, the Applicants provide even more disclosure of CG motif oligonucleotides in the specification as filed. Pages 5 and 9 of

the specification list twenty seven non-limiting examples of oligonucleotide sequences comprising CG motif(s) (SEQ ID NOs: 1-27). They further disclose embodiments where the CG motif is flanked by two purines immediately 5' to the motif and two pyrimidines immediately 3' to the motif. The embodiments on page 8 also provide details about backbones and lengths of oligonucleotides comprising CG motifs. In fact, the specification teaches most if not all of the details that the Examiner cites from the various articles. The Examiner notes that the art teaches that the CpG dinucleotides are unmethylated. The specification taught this design feature (which has been added to the claims since it does not change the scope of the claims). The Examiner notes that the art teaches that the oligonucleotide has to be at least 6 nucleotides. The specification taught this design feature (which again has been added to the claims since it does not change the scope of the claims). The Examiner notes that art teaches that the ODN has to be stabilized by phosphorothioate linkages. The specification taught this design feature (which again has been added to the claims).

Therefore, the Applicants respectfully assert that the instant specification and the information available in the art provide more than sufficient detail necessary to design suitable oligonucleotides comprising at least one CG motif.

ii. Immuno-stimulatory effects of adjuvant combinations

The Examiner alleges that the disclosure fails to provide adequate guidance pertaining to those immuno-stimulating adjuvants that can reasonably be expected to produce a synergistic immune response when combined with another adjuvant. The Examiner points out the unpredictability of the synergistic effect of combinations of adjuvants and alleges that it would require undue experimentation by a skilled artisan to practice the claimed invention. However, the oil-in-water adjuvants disclosed in the specification share a common mode of evoking an immune response, which is demonstrated by the data showing similar levels of protection produced by three oil-in-water adjuvants: CFA, MF59, and IFA (Table 2 in specification). Similarly, oligonucleotides comprising at least one CG motif also share a common mode of action in eliciting an immune response. As discussed above, Krieg *et al*. taught that immunostimulatory CpG oligonucleotides all

work by a common mode of action to stimulate a T_H1 response. Given the common mode of action of oil-in-water adjuvants and the common mode of action of oligonucleotides comprising at least one CG motif, one of skill in the art would not need to engage in undue experimentation to test the immuno-stimulatory effects of members of either class of adjuvants. Moreover, the specification clearly describes a working example demonstrating the superior protective response to a given bacteria when a particular antigen is combined with one exemplary oil-in-water adjuvant CFA and an oligonucleotide comprising at least one CG motif (Tables 1 and 2 in the specification).

Because of the common mode of action within each of the two classes of adjuvants, an example of the superior protection produced by one combination of the two types of adjuvants is sufficient to support the claims.

Therefore, the applicants assert that undue experimentation would not be required given the working example in the specification showing that an adjuvant in each class work together to provide a superior immune response to *Neisseria*. Applicants thus respectfully request that the Examiner withdraw the enablement rejections.

II. Incorporation by reference

The Examiner has noted that the specification includes incorporations by reference. Applicants thank the Examiner for noting the incorporations by reference. In the event that the referenced subject matter is demonstrated to be essential, Applicants will incorporate the subject matter as appropriate.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002102200**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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